REMARKS

Reconsideration is requested.

Claims 1-113 have been canceled, without prejudice.

Claims 114-128 have been added and are pending. Support for the revised claims may be found throughout the specification. No new matter has been added.

Claim 114 refers to TSH (Thyroid-Stimulating Hormone) to correct an inadvertent typographical error. Claim 114 also refers to antibodies elicited against the first glycoprotein binding to the second glycoprotein with an affinity higher than the binding affinity of said antibodies to the first glycoprotein.

The claims are believed to read on the previously-elected subject matter.

The applicants submit that an International Search Report is appropriate to be listed on the face of a U.S. Patent, as evidenced by the face of any of the 55,046 U.S. Patent issued by the U.S. Patent Office since 1976 which contain the phrase "International Search Report" in the "Other References" listing on the face. The following is a listing of the first 50 U.S. Patent Nos. and titles returned in a search of the U.S. Patent Office on-line "Quick " Search for "International Search Report" under Other References.

	PAT. NO.	Title
1	7,594,270	Threat scoring system and method for intrusion detection security networks
2	7,594,269	Platform-based identification of host software circumvention
3	7,594,263	Operating a communication network through use of blocking measures for responding to communication traffic anomalies
4	7,594,262	System and method for secure group communications
5	7,594,250	Method and system of program transmission optimization using a redundant

transmission sequence

6 7,594,236 T Thread to thread communication

7 7,594,232 T Intelligent memory device for processing tasks stored in memory or for storing data in said memory

8 7,594,227 T Dependency graph parameter scoping

9 7,594,224 T Distributed enterprise security system

10 7,594,220 T Configuration diagram with context sensitive connectivity

11 7,594,196 T Block interstitching using local preferred direction architectures, tools, and apparatus

12 7,594,151 T Reverse link power control in an orthogonal system

13 7,594,147 T Method and apparatus for recording data on and reproducing data from a recording medium and the recording medium

14 7,594,135 T Flash memory system startup operation

15 7,594,122 T Method of determining whether a test subject is a specific individual

16 7,594,116 T Mediated key exchange between source and target of communication

17 7,594,113 T Identification information protection method in WLAN inter-working

18 7,594,112 T Delegated administration for a distributed security system

19 7,594,097 T Microprocessor output ports and control of instructions provided therefrom

20 7,594,094 T Move data facility with optional specifications

21 7,594,079 T Data cache virtual hint way prediction, and applications thereof

22 7,594,055 T Systems and methods for providing distributed technology independent memory controllers

23 7,594,044 T Systems and methods of processing I/O requests in data storage systems

24 7,594,018 T Methods and apparatus for providing access to persistent application sessions

25 7,594,015 T Grid organization

26 7,594,011 T Network traffic monitoring for search popularity analysis

27 7,593,999 T Automotive telemetry protocol

28 7,593,973 T Method and apparatus for transferring snapshot data

29 7,593,965 T System of customizing and presenting internet content to associate advertising therewith

30 7,593,955 T Generation of aggregatable dimension information within a multidimensional enterprise software system

31 7,593,953 T Table lookup mechanism for address resolution

32 7,593,951 T Application programming interface for centralized storage of principal data

33 7,593,938 T Systems and methods of directory entry encodings

34 7,593,936 T Systems and methods for automated computer support

35 7,593,931 T Apparatus, system, and method for performing fast approximate computation of

statistics on query expressions
36 7,593,918 T Enterprise medical imaging and information management system with enhanced communications capabilities
37 7,593,915 T Customized multi-media services
38 7,593,909 T Knowledge representation using reflective links for link analysis applications
39 7,593,905 T Method of combinatorial multimodal optimisation
40 7,593,891 T Credit score simulation
41 7,593,889 T System and method for processing data pertaining to financial assets
42 7,593,887 T System and method for analyzing and displaying security trade transactions
43 7,593,885 T Materials supply contract system and method
44 7,593,883 T Financial activity based on tropical weather events
45 7,593,879 T System and method for using diversification spreading for risk offset
46 7,593,877 T System and method for hybrid spreading for flexible spread participation
47 7,593,871 T Multiple price curves and attributes
48 7,593,866 T Introducing a fixed-price transaction mechanism in conjunction with an auction transaction mechanism
49 7,593,824 T System and method for automation of hardware signal characterization and signal integrity verification
50 7,593,822 T Battery monitor

Return of a completely initialed copy of the previously-filed PTO 1449 Form is requested.

The objection to claim 101 is moot in view of the above. The objected-to term has been corrected in the new claims. No new matter has been added

The objection to claim 104 is moot in view of the above. The objected-to term or phrase has been corrected in the new claims.

The objection to claim 105 is moot in view of the above. The objected-to term or phrase has been corrected in the new claims.

The objection to claims 112-113 is moot in view of the above. The objected-to term or phrase has been repeated in the new claims.

The Section 112, first paragraph "written description", rejection of claims 101-113 is moot in view of the above. The claims have been revised to obviate the inadvertent typographical error which is the basis of the rejection. The claims are supported by an adequate written description.

The Section 112, second paragraph, rejection of claims 110-113 is moot in view of the above amendments. The claims are submitted to be definite in that the result of preamble of claim 114 is achieved as a part of the claimed process. Moreover, the recitation of the objected-to term has not been repeated in the new claims.

The following Section 103 rejections are moot in view of the above:

the Section 103 rejection of claims 101-108 and 110-112 over Papandreou (Molecular and Cellular Endocrinology 73:15-26, 1990), Kashiwai (Journal of Immunological Methods 143:25-30, 1991), Schaaf (Molecular and Cellular Endocrinology 132:185-194, 1997) and Szkudlinski (Endocrinology 133(4):1490-1503, 1993);

the Section 103 rejection of claim 109 over Papandreou, Kashiwai, Schaaf, Szkudlinski and Legaingneur (Journal of Biological Chemistry 276(24):21608-21617, 2001); and

the Section 103 rejection of claim 113 over Papandreou, Kashiwai, Schaaf, Szkudlinski, Zerfaoui (European Journal of Clinical Chemistry Clinical Biochemistry 34:749-753, 1996) and Fionnuala (Molecular Biotechnology 12:203-206, 1999).

The claims are patentable over the cited combinations of art. Consideration of the following in this regard is requested.

The claimed invention describes a process for screening known antibodies specifically recognizing pituitary or blood TSH and being able to specifically recognize, with a better affinity than the affinity for pituitary or blood TSH, at least one specific glycoform of recombinant TSH produced in mammal cells, said specific glycoform being more sialylated and less fucosylated and more or less branched.

To carry out the process according to the invention, the inventors have purified recombinant TSH from mammal cells (which is present in a mixture of many glycoforms) and have modified the glycosylation status of said glycoforms of TSH in order to specifically isolate recombinant TSH which is more sialylated and less fucosylated and more or less branched.

Therefore, a detailed process according to the invention comprises the following steps: (a) a step of checking that the antibodies elicited against the pituitary TSH bind to the recombinant TSH, (b) a step of classifying the antibodies to be screened in pools, each pool being characterized in that two antibodies selected from a same pool can not bind to the same glycoprotein at the same time, (c) a step of determination of the binding between: antibodies directed against pituitary TSH, and at least one glycoform of recombinant TSH, said glycoform of recombinant TSH being obtained by at least one fractionation and or at least one enzymatic modification in order to obtain a glycoform which is more sialylated, less fucosylated and more or less branched than the recombinant TSH, and (d) detecting the interaction between said antibody directed against pituitary TSH and said glycoform of said recombinant TSH.

Papandreou *et al.* teach a process for screening glycoform specific antibodies directed against native TSH and deglycosylated, or naturally glycosylated TSH. Papandreou *et al.* teach that modification in the glycosylation pattern of TSH may profoundly modify the interaction with specific antibodies.

Kashiwai *et al.* teach a method for screening antibodies that recognize recombinant TSH produced in CHO cells, and compare the binding of such antibodies with that of native (pituitary) TSH.

Schaaf *et al.* teach a method for producing recombinant TSH in CHO or COS cells, and the glycosylation of the rTSH produced is compared to the glycosylation of native TSH. Moreover, Schaaf *et al.* teach that sialylated and unsialylated TSH produced in CHO have an higher potency to stimulate cAMP, and that unfucosylated TSH are strong stimulator of cAMP release.

Szkudlinski *et al.* teach a method for producing recombinant TSH in CHO cells to overcome the difficulty of the native TSH purification. Moreover, Szkudlinski *et al.* teach that recombinant TSH is more sialylated than native pituitary TSH which is sulphated. This high degree of sialylation appears to be correlated with longer half life of TSH.

Papandreou *et al.* do not teach or suggest a process for screening specific TSH antibodies able to recognize recombinant TSH having a glycosylation pattern as follows: more sialylated, more branched and less fucosylated.

Therefore, from the teaching of Papandreou *et al.*, an ordinarily skilled person would not have been led to make a process for screening antibodies interacting with

native TSH that are able to specifically interact with glycoform of a recombinant TSH, with an affinity higher that the affinity for native TSH, as claimed.

Moreover, as mentioned in page 27, second column, paragraph "Binding activity to each epitope", Kashiwai *et al.* teach that the binding activities of rhTSH at α-1 epitope were lower that of the reference hTSH, although their activities at other epitopes were almost identical. Further, in page 28, first column, paragraph "Immunoassay", Kashiwai *et al.* teach that the recognition by four commonly used kits for hTSH were regarded "virtually identical" for rhTSH and native TSH.

Schaaf *et al.* also teach in page 187, first column, in the "Immunometric assays" paragraph, that there is a possibility that the antibodies do not recognize all TSH isoforms. Therefore, Schaaf *et al.* suggest that the antibodies used, i.e. commercial antibodies used in TSH sandwich ELISA, can possibly be inefficient for recognizing glycoform of recombinant TSH.

Moreover Papandreou *et al.* teach that TSH β subunit, which is the specific subunit of TSH, harbour most of the glycosylation dependant epitopes, and also teach that deglycosylation of TSH drastically modify the immunoreactivity of antibodies directed against TSH, conducting to a loss of antibody binding.

Finally, Szkudlinski *et al.* do not mentioned or suggest that glycoform of recombinant TSH have a better affinity for the antibodies directed against pituitary TSH.

It was known at the date of the invention that recombinant TSH which is hypersialylated has an affinity for antibodies which is lower compared affinity for pituitary TSH (see for instance, the abstract of the attached Thotakura *et al.*

Endocrinology. 1991 Jan;128(1):341-8). It was also known at the filing date that commercial antibodies (i.e. known antibodies) directed against TSH are not sensitive to changes in carbohydrate structure of TSH, i.e., said commercial antibodies recognize both recombinant and pituitary TSH with the same affinity. (see for instance, the attached abstract of Szkudlinski *et al.* PNAS. 1995 Sept; vol 92 :9062-9066).

Consequently, from all the above, at the time of the invention, the ordinarily skilled person would not have been led from a combination of the cited art to have made the claimed invention to screen antibodies directed against pituitary TSH to select antibodies having a better affinity for glycoform of recombinant TSH, since for example it was not appreciated that recTSH was hyperreactive to antibodies.

The ordinarily skilled person would not have been motivated by the cited art to have screened known antibodies, as claimed, since at least three of the cited documents (Papandreou *et al.*, Kashiwai *et al.* and Schaaf *et al.*) teach that the antibodies directed against pituitary TSH are less efficient, or have at most an equivalent efficiency, for glycoform of recombinant TSH.

Since Thotakura *et al.* teach that "The immunologic activity and porcine TSH receptor-binding activity of the preparation of recombinant hTSH were 3- to 4-fold lower than those of a standard pituitary hTSH" (see abstract), the ordinarily skilled person would not have been led to modify recombinant TSH, in particular by adding sialic acid with α sialyltransferase, to screen antibodies for a better affinity in binding such recombinant TSH.

Szkudlinski *et al.* and Schaaf *et al.* teach methods for purifying, or isolating, specific glycoform of recombinant TSH, using lectin fractionation or enzymatic modifications.

However, since Papandreou *et al.*, Kashiwai *et al.* and Schaaf *et al.*, and also Thotakura *et al.*, teach that it is not expected to obtain antibodies having a better affinity for glycoform of recombinant TSH compared to the affinity for pituitary TSH, the ordinarily skilled person would not have been led by the art of record to have made the claimed invention.

Therefore, the teaching of Papandreou *et al.*, in view of Szkudlinski *et al.*, Kashiwai *et al.* and Schaaf *et al.*, also in view of Thotakura *et al.*, would have taught away from the claimed process.

The Federal Circuit has explained that

> "A reference may be said teach away when a person of ordinary skill, upon the reading reference, would be discouraged from following the path set out in the reference, or would be led in direction divergent from the path that was taken by the applicant". See In re Gurley 31 USPQ2d 1130 (Fed. Cir. 1994).

The teaching of Papandreou *et al.* in view of Kashiwai *et al.*, Schaaf *et al.* and Szkudlinski *et al.* would have discouraged the ordinarily skilled person from making a screening process, as claimed.

The claims would not have been obvious in view of the cited art.

Legaigneur *et al.* teach a truncated ST6GalI sialyltransferase of its first N-terminus amino acids up to 100. Legaigneur *et al.* teach that such fusion has an increased sialyltransferase activity until 80 amino acids are deleted.

The Examiner is understood to believe that it allegedly would have been obvious to have replaced the sialytransferase taught by Szkudlinski *et al.* by the truncated sialyltransferase taught by Legaigneur *et al.*

The applicants submit however that since the ordinarily skilled person would have been discouraged from screening antibodies having a better affinity for glycoform of recombinant TSH compared to the affinity for pituitary TSH, as explained above, the ordinarily skilled person would not have been motivated to use the shortened ST6Gall sialytransferase in a process of the claimed invention. Legaigneur *et al.* fails to cure the deficiencies noted above with regard to the art of record.

The applicants note in this regard that Thotakura *et al.*, teach that the oversialylated recombinant TSH has an immuno reactivity reduced compared to the immunoreactivity of pituitary TSH.

The claimed invention would not have been obvious over the cited art.

Zerfaoui *et al.* teach enzyme-linked immunosorbent assay for comparing recognition of pituitary TSH and recombinant TSH before and after desialylation.

Fionnuala *et al.* teach a sandwich assay using antibody directed against a glycoprotein and a lectin recognising specific glycoform.

The disclosures of Zerfaoui *et al.* and Fionnuala *et al.* fail to cure the deficiencies of the above noted art of record.

The Examiner is understood to believe that it would have been obvious for a person of ordinary skill to have made a process for screening antibodies elicited against pituitary TSH to obtain antibodies directed against glycoform of recombinant TSH by

adapting the assay proposed by Fionnuala *et al.* and compare affinity of said antibodies before and after desialylation as taught by Zerfaoui *et al.*

As discussed above, the applicants believe that the art of record teaches away from the claimed invention.

Moreover, Zerfaoui *et al.* teach a comparison of antibodies binding before and after desialylation of TSH. Zerfaoui *et al.*, in figures 3 and 4, page 752, that depending on the antibody used, the recognition of asialo pituitary and recombinant TSH is equal or less efficient than the recognition of the calibrant (pituitary TSH international Standard).

Thus, from the teaching of Zerfaoui *et al.*, the ordinarily skilled person would not have been motivated to have modified the sialyl content of recombinant TSH to screen antibodies, since modification (i.e. desialylation) has been widely shown to decrease antibody reactivity. Further, Fionnuala *et al.* teach a sandwich assay using antibody directed against a glycoprotein and a lectin recognising specific glycoform. Fionnuala *et al.* teach, on page 203 in the second paragraph of the introduction, that "we used this principle (i.e. principle of figure 1) to develop a method for the measurement of asialo-α1-chymotrypsin ...". Moreover, Fionnuala *et al.* teach that for the implementation of the antibody-lectin assay, it is essential to desialylate the glycoprotein used as standard.

The ordinarily skilled person adapting the Fionnuala *et al.* assay to develop an assay using two antibodies would have been led to desialylate a calibrant protein (first glycoprotein). However, as taught by Zerfaoui *et al.* for instance, such modification will decrease the binding capacity of the screened antibodies. The applicants believe

therefore that the combination of Fionnuala *et al.* and Zerfaoui *et al.* would have also taught away from the claimed invention..

The claimed invention would not have been obvious in view of the art of record.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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